Tetrahedron Letters,Vol.29,No.12,pp 1341-1342,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

THE SYNTHESIS OF 1H-PYRAZOL-4-OLS FROM 2-(2-ALKYLIDENEHYDRAZINO)ACETIC ACIDS

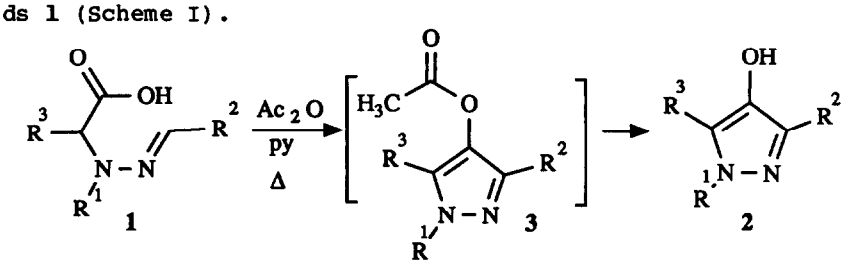
Garry M. Pilling, Rebecca H. Bell, and Robert E. Johnson*
Sterling-Winthrop Research Institute
Rensselaer, NY 12144

Abstract: A new general method for synthesizing 1H-pyrazol-4-ols by cyclizing 2-(2-alkylidenehydrazino)acetic acids with acetic anhydride in pyridine is reported.

The synthesis of 1H-pyrazol-4-ols has only recently yielded to a general approach.[1] In that synthesis, 1H-pyrazol-4-ols were prepared by the acid catalyzed condensation of hydrazones with glyoxals in poor to exceptional yields (14-100%). Prior synthetic reports, though practical for specific substitution patterns, were compromised by a lack of generality[2-9] and regiospecificity.[8,10]

We have discovered another general synthesis of 1H-pyrazol-4-ols that gives improved yields in certain examples (see Table I) and thus is complementary to other syntheses. This method is based upon our observation that acetic anhydride in pyridine will induce cyclization of 2-(2-alkylidenehydrazino)-acetic acids **1** (Scheme I).

Scheme I:



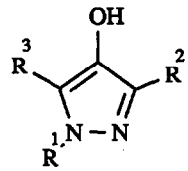
Generally, the precursor hydrazones **1** were prepared in 56-76% yields by the method reported for **1** (R^1=CH_3, R^2=R^3=C_6H_5)[11] by alkylation of the appropriate hydrazines with 2-bromoacetic acids, and then condensation of the resultant hydrazinoacetic acids with aldehydes.

The preparation of **2** (R^1=CH_3, R^2=R^3=C_6H_5) was by the following procedure. Other examples of structure **2** were prepared in a similar manner, and their yields and melting points are presented in Table I. The intermediate acetates **3** were not isolated, but were directly converted to 1H-pyrazol-4-ols **2** by mild basic hydrolysis.

A mixture of 30 mL pyridine, 2.1 mL (0.22 mol) acetic anhydride, and 0.9 g (0.11 mol) anhydrous sodium acetate was stirred at room temperature for 15 min. (The sodium acetate was used only if the hydrazone **1** was a salt.) Addition of 3.0 g (0.010 mol) **1** (R^1=CH_3, R^2=R^3=C_6H_5) HCl was followed by heating the magnetically stirred mixture on a steam bath for one hour. The volatiles were removed under reduced pressure, and to the residue was added 50 mL MeOH and 5 g

K_2CO_3. After stirring this mixture overnight, 50 mL EtOAc and 50 mL H_2O were added. The aqueous layer was brought to pH 8 most expeditiously by adding 3N HCl to pH 5 and then back titrating to pH 8 with solid $NaHCO_3$. The EtOAc layer was separated, dried ($MgSO_4$) and concentrated to give 2.5 g of a solid which was crystallized from CH_3CN to give 1.93 g (77%) of **2** (R^1=CH_3, R^2=R^3=C_6H_5).

TABLE I: Preparation of 1H-Pyrazol-4-ols **2** from Hydrazones **1**



					lit.	
R^1	R^2	R^3	% yield	m.p. (°C)	% yield	m.p. (°C)
CH_3	C_6H_5	C_6H_5	77	173-174	86[a]	142-149[a]
CH_3	CH_3	C_6H_5	38	156-157	15[a]	149-154[a]
C_6H_5	C_6H_5	CH_3	73	146-147	35[a]	119-133[a]
C_6H_5	C_6H_5	C_6H_5	63	154-156	70[a]	148-149[a]
C_6H_5	HCO	H	75	143-146	42[a]	132-136[a]
C_6H_5	C_6H_5CO	H	76	105-106	84[a]	101-105[a]
C_6H_5	COOEt	H	85	71-75[c]	[d]	84[b]

[a]Reference 1. [b]L. Wolff, A. Luttringhaus, and E. Fertig, Ann., **313**, 1 (1900). [c]Recrystallized from EtOH, mp. 83.5-85°C. [d]No yield reported.

References:

1. M. Begtrup and H.P. Nytoft, J. Chem. Soc. Perkin Trans. I, 81 (1985).
2. R.H. Wiley and P. Wiley, "Pyrazolones, Pyrazolidones, and Derivatives," in "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience Publishers, New York, NY, 1964, Ch 3.
3. M.J. Nye and W.P. Tang, Can. J. Chem., **51**, 338 (1973), **48**, 3563 (1970).
4. P.J. Fagan, E.E. Neidert, M.J. Nye, M.J. O'Hare, and W.P. Tang, Can. J. Chem., **57**, 904 (1979).
5. J. Farkas and Z. Flegelova, Tetrahedron Lett., 1591 (1971).
6. F.S.G. Soliman and R.M. Shafik, Pharmazie, **30**, 436 (1975).
7. M. Albrand and S. Gelin, Synthesis, 1030 (1983).
8. J.P. Freeman, J.J. Gannon, and D.L. Surbey, J. Org. Chem., **34**, 187 (1969).
9. C. Sabate-Alduy, J. Bastide, and P. Bercot, Bull. Soc. Chim. France (Chim. Mol.), 1841 (1976).
10. B.L. Walworth, U.S. Pat. 4,000,301 (1976).
11. R. Monguzzi, G. Libassi, M. Pinza, and G. Pifferi, Il Farmaco Ed. Sci., **31**, 549 (1976).

(Received in USA 24 November 1987)